Synthesis of New Chiral Calix[4]crown Containing (*R*)-Cysteine

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Three new chiral heterocalix[4]crowns containing aza thio atoms bearing two chiral sites provided by (*R*)-cysteine ester were synthesized. All new compounds were characterized by ^{1}H NMR, MS and elemental analysis.

Keywords Chiral calix[4]crown, synthesis, (*R*)-cysteine

Introduction

Chiral recognition or discrimination is one of the main goals in areas like host-guest chemistry and biomimetic chemistry,[1] and the preparation and properties of chiral ligands have attracted considerable attention in the fields of organic, biological, and medicinal chemistry. Calixarenes are useful building blocks in the design of novel host molecules for cations,[2] anions,[3] and neutral molecules.[4] Receptors with a chiral cavity are of particular interest for chiral recognition and chiral catalysis, and this has led to the development of chiral calixarenes. Various attempts have been made to obtain chiral calixarene including some inherent chiral calixarene derivatives[5] and some attachment of chiral groups to the lower- or upper-rim of calixarene.[6] In order to achieve the chirally modified macrocyclic ligands, amino acids or peptides may be employed as chiral sources in building the desired molecules because of their accessibility and biological relevance. Although the syntheses of calixarene receptors functionlized at the upper[7]- or lower-rim[8] with amino acid or peptide units have been reported, only very few multi-cyclic receptor systems combining both cyclopeptide and calixarene have been synthesized,[6b,6c] and the profound potential of this type of chiral multi-cyclic compound in both chemistry and life sciences is still far uncultivated. In this paper, we report the first synthesis of new chiral calix[4]crown containing (*R*)-cysteine, **9a—c**. It is believed that these new chiral macrocyclic ligands may serve as good candidates in future studies of chiral recognition and chiral catalysis. The synthetic routine is shown in Scheme 1.

Results and discussion

Synthesis

One of the starting reagents, oligoethylene glycol dichlorides **2a—c**, was prepared from polyglycol **1** and thionyl chloride in the presence of pyridine as reported in the literature.[9] The *L*-cysteine was converted into the bridged bis-amino acid methyl ester dihydrochloride **5a—c** by treatment with bis-(2-chloroethyl)ether (**2a**), 1,2-bis(2-chloroethoxy)ethane (**2b**), bis-(2-chloroethoxyethyl)ether (**2c**), espectively, followed by esterification with thionyl chloride in methanol. In these reactions, oligoethylene glycol dichloride was added dropewise to the solution of (*R*)-cysteine in 2N NaOH and ethanol in ice-bath and stirred. After the addition, the mixture was stirred for 24 h at ambient temperature. Because compounds **4a—c** were subjected to oxidation, they were dissolved in dry chloroform and then dry HCl was ventilated into the solution, the white solid of bis-amino acid methyl ester dihydrochloride **5a—c** was obtained. Compounds **5a—c** should be kept in desiccator because they were easily hygroscopic.

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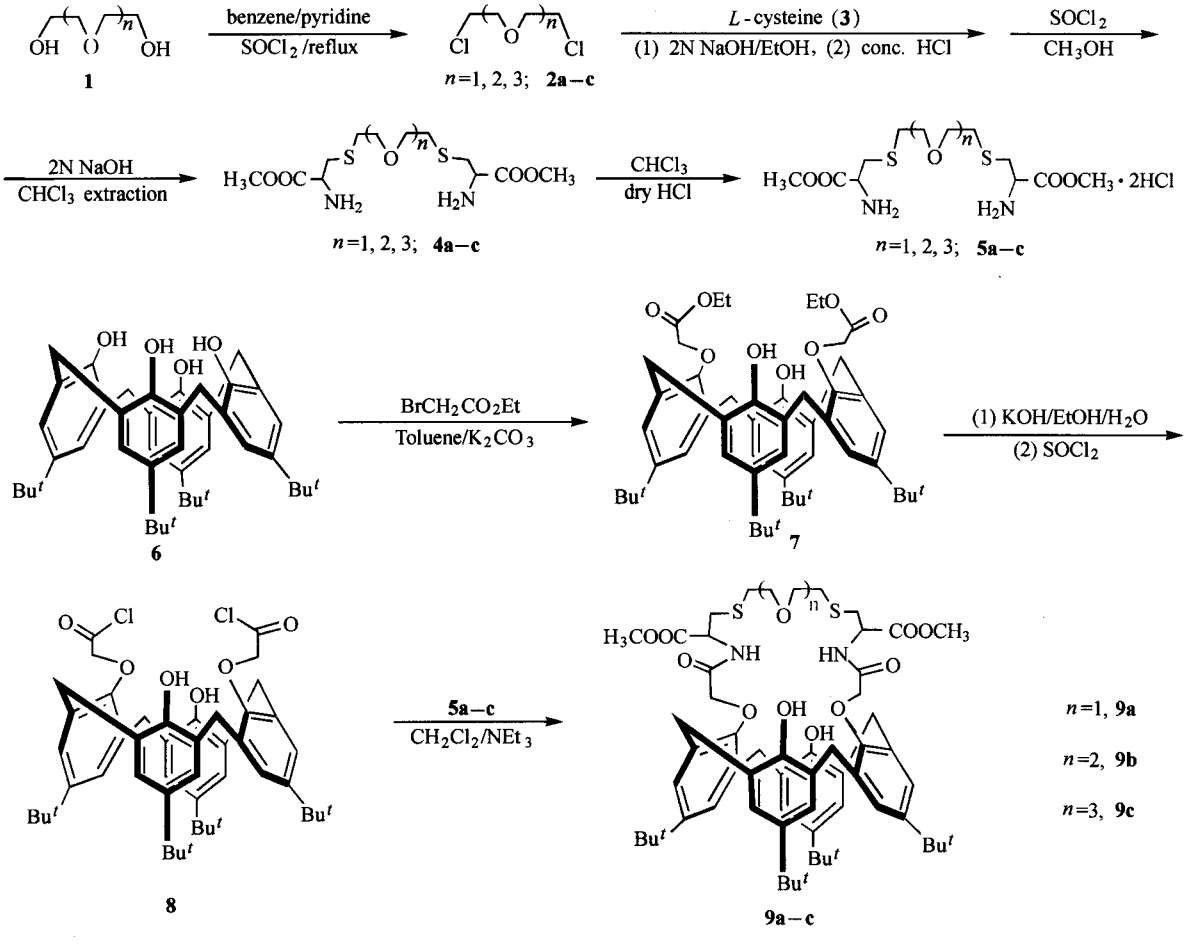
The other starting reagent, calix[4]arene diacide dichloride (**8**) was obtained from *p-tert*-butylcalix[4]-arene (**6**) according to a modified literature.[10] Toluene and KOH aq. were used here as the reaction solvent instead of acetone and NaOH aq., respectively, as in the literature case, because the former reaction progress and product yield were greatlyimproved. The reason may be due to the heterogeneous phase reaction in toluene in which the reaction progress was accelerated and the product yield was improved.

Scheme 1



As depicted in Scheme 1, coupling of compound **8** with **5a—c** in dichloromethane in the presence of excess triethylamine under dilution condition gave the corresponding new chiral heterocalix[4]crowns containing (*R*)-cysteine-ester **9a—c** (in 10—18% yields).

Structure and ^{1}H NMR *spectrum*

The chiral calix[4]crowns **9a—c** gave satisfactory elemental analysis results and the FAB-MS spectra indicated that they were '1 + 1' cyclization products. The ^{1}H NMR spectra of **9a—c** show two sets of doublets covering a range of δ 3.30—4.50 ppm (J = 12.8—13.8 Hz) for the bridged methylene protons. This demonstrated that all these compounds are in a cone conformation.

The ^{1}H NMR spectra of **9a—c** also exhibit two sets of doublets for the aromatic protons and one set of doublets for the $ArOCH_2$ protons. In the partial ^{1}H NMR spectrum of **9a** as shown in Fig. 1, we observed these signals that are due to $ArOCH_2$(a1, a2) and $ArCH_2Ar$ (b1, b2, b3, b4) protons, the OCH_2CH_2S(c1, c2) protons appeared in two multiplets covering a range of δ 3.70—3.96 ppm and the SCH_2CH (d1, d2) protons in the molecule **9a** appeared in two sets of double doublets. This splitting pattern may relate to the presence of the chiral moieties in the molecules because it is similar to what we observed in other chiral calix[4]arenes.[6b,7a]

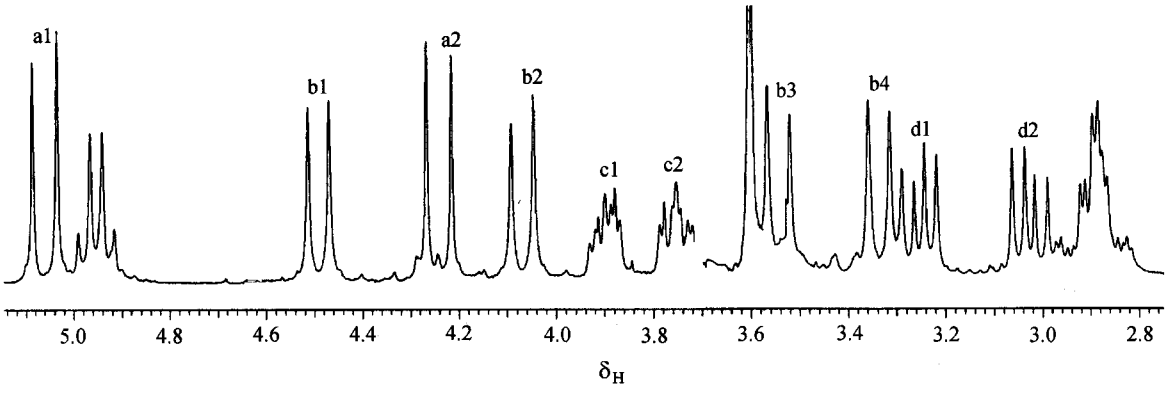


Fig. 1 ^{1}H NMR spectrum of compound **9a**.

Experimental

Apparatus

^{1}H NMR spectra were obtained on a Varian mercury VX-300 MHz spectrometer using deuteriochloroform as solvent and chemical shifts were given relative to TMS. Melting points were taken on a Rechert-7905 melting point apparatus. Mass spectra were recorded on a ZAB-HF-3F MS instrument. Elemental analyses were performed by the Perkin-Elmer 204 B elemental analysis apparatus. Optical rotations were measured on a Wzz-15 automatic polarimeter. Thin layer chromatography was carried out on silica gel (GH) and spots located with iodine vapor. Flash column chromatography was performed on silica gel (100—200 mesh) with chloroform (CH_3OH 5% *V/V*) and chloroform (ethyl acetate 10% *V/V*) as a mixture solvent for compounds **4a**—**c** and **9a**—**c**, respectively.

Chemicals and materials

Toluene was dried over sodium and distilled before use, dichloroform was refluxed with calcium hydride for 6 h and distilled before use, triethylamine was dried over potassium hydroxide pellets over night and distilled, and stored over KOH pellets, methanol was refluxed with magnesium and distilled before use, *L*-cysteine was obtained from biological technology company of Shanghai Lizhu-Dongfeng. *p-tert*-Butylcalix[4]arene was prepared according to literature procedure.[11]

Synthesis of the bridged bis-amino acid methyl esters **4a**—**c**

General procedure To an ice-cooled suspension of 4.0 g (33.0 mmol) of (*R*)-cysteine in 25 mL of 2N NaOH and 20 mL of ethanol, a solution of oligoethylene glycol dichloride (**2**, 16.0 mmol for **2a**—**c**) was added dropewise at 0℃, then after stirring for 24 h at ambient temperature, the reaction mixture was acidified cautiously with conc. HCl until pH = 9, the precipitate was filtered off, washed with ether and dried *in vacuo*, without further purification and characterization, then 2.0 g of the obtained bridged bis-amino acid hydrochloride was suspended in 40 mL of anhydrous methanol and cooled to 0℃ in ice-bath, 1.2 g (9.5 mmol) of $SOCl_2$ was added slowly with vigorous stirring. After addition, the reaction mixture was allowed to warm to r.t., stirred for 24 h, and the solvent was evaporated under vacuum. The obtained crude product was dissolved in water and basified cautiously with 2N NaOH till pH = 9. The solution was extracted with chloroform and purified by column chromatography with chloroform (CH_3OH 5% *V/V*) as mixture solvent, thus pure compounds **4a**—**c** were obtained.

Compound **4a** colorless thick liquid, yield 58%. δ_H: 3.74 (dd, J = 4.8, 4.2 Hz, 2H, CHN), 3.68 (s, 6H, OCH_3), 3.59—3.63 (m, 2H, OCH_2CH_2S), 3.55—3.59 (m, 2H, OCH_2CH_2S), 3.05 (dd, J = 4.8, 14.5 Hz, 2H, SCH_2CH), 2.88 (dd, J = 4.2, 14.5 Hz, 2H, SCH_2CH), 2.68—2.72 (m, 4H, $2SCH_2CH_2O$), 1.78 (s, 4H, $2NH_2$, after addition of D_2O, this peak disappeared). *m/z*(%): 340(M^+, 40). Anal. $C_{12}H_{24}N_2O_5S_2$. Calcd: C, 42.33; H, 7.12; N, 8.23. Found: C, 42.32; H, 7.41; N, 7.91.

Compound **4b** colorless thick liquid, yield,

64%. δ_H: 3.71 (dd, J = 4.5, 4.8 Hz, 2H, CHN), 3.65 (s, 6H, OCH_3), 3.61—3.65 (m, 4H, OCH_2CH_2O), 3.52—3.56 (m, 2H, OCH_2CH_2S), 3.48—3.52 (m, 2H, OCH_2CH_2S), 3.02 (dd, J = 4.5, 14.7 Hz, 2H, SCH_2CH), 2.79 (dd, J = 4.8, 14.7 Hz, 2H, SCH_2CH), 2.62—2.66 (m, 4H, $2SCH_2CH_2O$), 1.75 (s, 4H, $2NH_2$, after addition of D_2O, this peak disappeared). m/z(%): 384 (M^+, 60). Anal. $C_{14}H_{28}N_2O_6S_2$. Calcd: C, 43.72; H, 7.35; N, 7.29. Found: C, 43.70; H, 7.51; N, 6.97.

Compound **4c** colorless thick liquid, yield 54%. δ_H: 3.77 (dd, J = 5.1, 4.5 Hz, 2H, CHN), 3.73—3.77 (m, 4H, OCH_2CH_2O), 3.69—3.73 (m, 4H, OCH_2CH_2O), 3.69 (s, 6H, OCH_3), 3.63—3.68 (m, 2H, OCH_2CH_2S), 3.58—3.63 (m, 2H, OCH_2CH_2S), 3.07 (dd, J = 4.5, 14.8 Hz, 2H, SCH_2CHN), 2.87 (dd, J = 5.1, 14.8 Hz, 2H, SCH_2CHN), 2.77—2.85 (m, 4H, $2SCH_2CH_2O$), 1.79 (s, 4H, $2NH_2$, after addition of D_2O, this peak disappeared). m/z(%): 428(M^+, 55). Anal. $C_{16}H_{32}N_2O_7S_2$. Calcd: C, 44.83; H, 7.54; N, 6.54. Found: C, 44.80; H, 7.71; N, 6.48.

Synthesis of the calix[4] *crowns containing* (*R*)*-cysteine*, **9a—c**

General procedure A solution of calix[4]arene diacid dichloride **8** (2.0 mmol) in dry dichloromethane (100 mL) was added dropewise to a vigorous stirred and ice-cooled solution of *S*-alkylated cysteine ester hydrochloride **5** (2.0 mmol for **5a—c**) and triethylamine (9.0 mmol) in dry dichloromethane (500 mL), after addition the mixture was stirred overnight at ambient temperature followed by being washed sequentially with dilute hydrochloride, water, dilute sodium hydrogen carbonate solution and brine, then the organic phase was dried with anhydrous sodium sulfate. After filtration, the filtrate was evaporated and purified by column chromatography on silica gel (200—300 mesh) with chloroform (ethyl acetate 10% V/V) as mixture solvent, to give pure products **9a—c**.

Compound **9a** yield 11.5%. mp 136—138℃. $[\alpha]_D^{24}$ = +71.0 (c 0.006, $CHCl_3$). δ_H: 9.56 (d, J = 7.5 Hz, 2H, NHCH, after addition of D_2O, this peak disappeared), 7.66 (s, 2H, ArOH, after addition of D_2O, this peak disappeared), 7.10 (d, J = 2.4 Hz, 2H, ArH), 7.04 (d, J = 2.1 Hz, 2H, ArH), 6.96 (d, J = 2.1 Hz, 2H, ArH), 6.88 (d, J = 2.1 Hz, 2H, ArH), 5.06 (d, J = 15.6 Hz, 2H, $ArOCH_2$), 4.96 (q, J = 7.5 Hz, 2H, $NHCHCH_2S$), 4.49 (d, J = 13.2 Hz, 2H, $ArCH_2Ar$), 4.24 (d, J = 15.6 Hz, 2H, $ArOC_2$), 4.07 (d, J = 13.8 Hz, 2H, $ArCH_2Ar$), 3.84—3.94 (m, 2H, OCH_2CH_2S), 3.70—3.80 (m, 2H, OCH_2CH_2S), 3.60 (s, 6H, OCH_3), 3.54 (d, J = 13.2 Hz, 2H, $ArCH_2Ar$), 3.34 (d, J = 13.8 Hz, 2H, $ArCH_2Ar$), 3.25 (dd, J = 7.5, 14.1 Hz, 2H, SCH_2CH), 3.02 (dd, J = 7.5, 14.1 Hz, 2H, SCH_2CH), 2.84—2.96 (m, 4H, $2SCH_2CH_2O$), 1.26 (s, 18H, Bu^t), 1.03 (s, 18H, Bu^t). m/z(%): 1068 (M^+, 12). Anal. $C_{60}H_{80}N_2O_{11}S_2$. Calcd: C, 67.37; H, 7.55; N, 2.62. Found: C, 66.98; H, 7.84; N, 2.52.

Compound **9b** yield 18.0%. mp 121—123℃. $[\alpha]_D^{24}$ = +90.5 (c 0.009, $CHCl_3$). δ_H: 9.50 (d, J = 7.5 Hz, 2H, NHCH, after addition of D_2O, this peak disappeared), 7.60 (s, 2H, ArOH, after addition of D_2O, this peak disappeared), 7.13 (d, J = 2.1 Hz, 2H, ArH), 7.07 (d, J = 2.1 Hz, 2H, ArH), 6.81 (d, J = 2.1 Hz, 2H, ArH), 6.73 (d, J = 2.1 Hz, 2H, ArH), 5.10 (d, J = 15.6 Hz, 2H, $ArOCH_2$), 4.98 (q, J = 7.5 Hz, 2H, $NHCHCH_2S$), 4.35 (d, J = 12.8 Hz, 2H, $ArCH_2Ar$), 4.29 (d, J = 15.6 Hz, 2H, $ArOCH_2$), 4.04 (d, J = 13.6 Hz, 2H, $ArCH_2Ar$), 3.85—3.93 (m, 4H, OCH_2CH_2O), 3.78—3.85 (m, 2H, OCH_2CH_2S), 3.68—3.76 (m, 2H, OCH_2CH_2S), 3.50 (s, 6H, OCH_3), 3.36 (d, J = 12.8 Hz, 2H, $ArCH_2Ar$), 3.32 (d, J = 13.6 Hz, 2H, $ArCH_2Ar$), 3.27 (dd, J = 7.5, 14.2 Hz, 2H, SCH_2CH), 3.04 (dd, J = 7.5, 14.2 Hz, 2H, SCH_2CH), 2.86—2.94 (m, 4H, $2SCH_2CH_2O$), 1.12 (s, 18H, Bu^t), 0.98 (s, 18H, Bu^t). m/z(%): 1112 (M^+, 10). Anal. $C_{62}H_{84}N_2O_{12}S_2$. Calcd: C, 66.87; H, 7.62; N, 2.52. Found: C, 66.59; H, 7.72; N, 2.42.

Compound **9c** yield 14.0%. mp 115—117℃. $[\alpha]_D^{24}$ = +76.6(c 0.010, $CHCl_3$). δ_H: 9.52 (d, J = 7.5 Hz, 2H, NHCH, after addition of D_2O, thispeak disappeared), 7.58 (s, 2H, ArOH, after addition of D_2O, this peak disappeared), 7.12 (d, J = 2.1 Hz, 2H, ArH), 7.06 (d, J = 2.1 Hz, 2H, ArH), 6.98 (d, J = 2.1 Hz, 2H, ArH), 6.90 (d, J

=2.1 Hz, 2H, ArH), 5.08 (d, J = 15.6 Hz, 2H, $ArOCH_2$), 4.93—5.01 (m, 2H, $NHCHCH_2S$), 4.50 (d, J = 13.0 Hz, 2H, $ArCH_2Ar$), 4.25 (d, J = 15.6 Hz, 2H, $ArOCH_2$), 4.09 (d, J = 13.6 Hz, 2H, $ArCH_2Ar$), 3.85—3.93 (m, 4H, OCH_2CH_2O), 3.72—3.80 (m, 4H, OCH_2CH_2O), 3.60—3.69 (m, 4H, $2OCH_2CH_2S$), 3.59 (s, 6H, OCH_3), 3.52 (d, J = 13.0 Hz, 2H, $ArCH_2Ar$), 3.33 (d, J = 13.6 Hz, 2H, $ArCH_2Ar$), 3.05—3.22 (m, 4H, $2SCH_2CH$), 2.93—3.03 (m, 4H, $2SCH_2CH_2O$), 1.26 (s, 18H, Bu^t), 0.95 (s, 18H, Bu^t). m/z(%): 1154 (M^+, 7). Anal. $C_{64}H_{88}N_2O_{13}S_2$. Calcd: C, 66.40; H, 7.68; N, 2.42. Found: C, 66.36; H, 7.92 ; N, 2.14.

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